Review Article :

Periodontal ligament stem cell and dental pulp stem cell's therapeutic potential in Alzheimers disease- A systematic scoping review

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder affecting millions globally. Periodontal ligament stem cells (PDLSCs) and dental pulp stem cells (DPSCs) have shown promise beyond dental tissue regeneration, potentially offering therapeutic benefits for neurodegenerative disorders such as AD. This scoping review aimed to map the global evidence on the therapeutic effects of PDLSC and DPSC on AD, following the JBI methodology and Arksey and O'Malley's 2005 framework. Studies focused on PDLSC and DPSC in AD were included, excluding opinion papers and review articles. Comprehensive searches in PubMed, Web of Science, and SCOPUS up to October 30, 2024, yielded relevant studies, which were collated and managed using ENDNOTE 20. Data were extracted using online tool. The review aggregates current evidence on the therapeutic effects and mechanisms of PDLSC and DPSC in AD treatment, highlighting potential benefits and identifying literature gaps. Despite promising findings, further research is necessary to substantiate these benefits. The review also suggests conceptual and methodological strategies for future studies to address limitations and clarify the roles of these stem cells in AD treatment.

Keywords:

Alzheimer's disease; neurogenesis; Stem cells; Periodontal ligament; Dental pulp

Introduction:

Stem cells play a pivotal role in neuroscience, offering immense potential for understanding brain development, repairing damaged neural tissue, and treating neurological disorders. These versatile cells possess the remarkable ability to self-renew and differentiate into various cell types found in the nervous system, including neurons, astrocytes, and oligodendrocytes[1]. Stem cells can be classified based on their differentiation capacity and origins. Differentiation capacity categorizes stem cells into totipotent, pluripotent, multipotent, oligopotent, and unipotent types [2]. Totipotent stem cells can give rise to any cell type in an embryo and extra-embryonic tissues, while pluripotent stem cells are limited to the three embryonic germ layers. Multipotent stem cells can differentiate into one germ line tissue, and oligopotent/unipotent stem cells are found in adult organ tissues committed to spescific cell lineages. Stem cells can also be classified based on their origins, such as embryonic stem cells derived from embryos and adult stem cells found in adult tissues [3,4].

Recently, researchers identified five distinct cell populations in dental tissues that exhibit mesenchymal stem cell characteristics. These include dental pulp stem cells, stem cells from human exfoliated deciduous teeth, periodontal ligament stem cells, dental follicle precursor cells, and stem cells from the apical papilla. Each of these dental stem cell populations has unique characteristics and advantages [5].

Stem cells originating from the oral cavity, which are derived from migrating neural crest cells, represent a multipotent cell population. These cells originate from the lateral ridges of the neural plate during craniofacial development [6]. Neural crest cells are considered to be the fourth germ layer as they exhibit stemness features and multipotency, play a crucial role in tooth organ development and contribute to craniofacial bone formation [7]. Periodontal ligament stem cells (PDLSCs) and dental pulp stem cells (DPSCs) are derived from neural crest cells. which arise during early embryonic development, migrate to various parts of the body and give rise to a variety of cell types, including those that form the dental tissues such as the periodontal ligament and dental pulp. Consequently, PDLSCs and DPSCs retain characteristics of their neural crest origins [8].

Mesenchymal stem cells are a type of multipotent adult stem cell that can differentiate into various cell types of mesodermal origin, such as osteoblasts, adipocytes, and chondrocytes [9]. Mesenchymal stem cells (MSCs) have garnered significant interest

in neuroscience due to their potential therapeutic applications in treating neurological disorders and injuries. While originally identified for their ability to differentiate into mesodermal lineage cells, including bone, cartilage, and adipose tissue, MSCs also exhibit neuroprotective, immunomodulatory, and regenerative properties [10]. MSCs can migrate to sites of neural injury or inflammation, where they secrete various growth factors, cytokines, and extracellular vesicles that promote tissue repair, modulate immune responses, and support neuronal survival and function[11]. Moreover, MSC-derived exosomes have emerged as promising vehicles for delivering therapeutic cargoes to the central nervous system[12,13]. Harnessing the neuroprotective and reparative potential of MSCs offers novel strategies for treating neurodegenerative diseases, stroke, spinal cord injury, and other neurological conditions, representing a burgeoning field at the intersection of stem cell biology and neuroscience [13].

Periodontal ligament stem cells (PDLSCs) and dental pulp stem cells (DPSCs) are considered mesenchymal stem cells (MSCs). Both exhibit characteristics of mesenchymal stem cells, originating from the neural crest during embryonic development [14,15]. They possess regenerative potential, able to differentiate into various cell types and promote tissue repair in dental and periodontal tissues[16-18]. Additionally, they display immunomodulatory properties and have been investigated for applications beyond dentistry, including treating systemic diseases and injuries affecting other tissues [19] Despite some differences in gene expression and microenvironmental influences, their commonalities make them valuable for studying stem cell biology and developing therapeutic interventions. Furthermore, harvesting DPSCs and PDLSCs is easier and less invasive than obtaining other MSCs because they can be collected from extracted teeth or tissues around teeth during routine dental procedures, making them more accessible and causing less discomfort to patients compared to bone marrow or adipose tissue extraction, while also avoiding ethical issues by using biological material that would otherwise be discarded [20-23].

Periodontal ligament stem cells (PDLSCs):

The periodontal ligament (PDL) is a complex, fibrous connective tissue that surrounds the tooth root and lines the alveolar bone sockets. It plays a crucial role in tooth support, proprioception, and shock absorption during mastication. Comprising a heterogeneous cell population embedded in an extracellular matrix rich in collagen

fibers, the PDL serves as a dynamic interface between the tooth and its surrounding bone [24,25]. In 2004, Seo and colleagues first isolated and characterized PDLSCs from human third molars, demonstrating their capacity for self-renewal and multilineage differentiation potential[26]. Subsequent studies further elucidated the phenotypic and functional properties of PDLSCs, confirming their expression of mesenchymal stem cell markers such as STRO-1, CD146, and CD90, and their ability to differentiate into osteoblasts, adipocytes, chondrocytes, and other cell lineages [27-30].

Unlike bone marrow-derived mesenchymal stem cells (BMSCs), which are commonly used in regenerative medicine, PDLSCs reside in a unique microenvironment rich in mechanical stress, inflammatory mediators, and neurovascular elements. This niche environment influences the properties and behaviour of PDLSCs, enhancing their regenerative potential and responsiveness to external stimuli [31]. In vitro studies have demonstrated their ability to regenerate periodontal tissues, including cementum, periodontal ligament, and alveolar bone, offering potential treatments for periodontal diseases and tooth loss [32,33]. Moreover, preclinical and clinical studies have explored the use of PDLSCs in tissue engineering approaches for craniofacial defects, orthopaedic injuries, and neurological disorders, highlighting their versatility and therapeutic versatility [8,34]. PDLSCs exert their regenerative effects through various mechanisms, including paracrine signalling, immunomodulation, and extracellular matrix remodelling. Moreover, their interactions with neighbouring cells, such as fibroblasts, osteoblasts, and endothelial cells, play crucial roles in orchestrating tissue repair processes [35-37]. Periodontal ligament stem cells represent a promising source of multipotent stem cells with wide-ranging implications for regenerative medicine, tissue engineering, and clinical dentistry [8].

Dental Pulp Stem Cells:

The dental pulp, situated in the core of the tooth, comprises a heterogeneous mixture of cells, blood vessels, nerves, and extracellular matrix components. It serves as a vital component of the dental organ, contributing to tooth development, maintenance, and repair. Enclosed within the mineralized dental tissues (enamel, dentin, and cementum), the dental pulp contains a reservoir of stem and progenitor cells that are capable of self-renewal and differentiation into specialized cell types [38]. The identification of DPSCs dates back to the early 2000s when Gronthos and colleagues first isolated and characterized these cells from the pulp tissue of human third molars[39].

Subsequent studies confirmed the presence of DPSCs in various tooth types, including deciduous teeth, permanent teeth, and supernumerary teeth. DPSCs were found to exhibit mesenchymal stem cell-like properties, expressing surface markers such as STRO-1, CD146, CD90, and CD73, and demonstrating multipotent differentiation potential [40-42].

Located within the dental pulp, a soft connective tissue housed in the pulp cavity of teeth, DPSCs exhibit unique properties that make them highly attractive for various biomedical applications, including dental regeneration, craniofacial repair, and systemic disease treatments [38]. Unlike bone marrow-derived mesenchymal stem cells (BMSCs), which are commonly utilized in regenerative medicine, DPSCs exhibit higher proliferative capacity, enhanced immunomodulatory properties, and greater resistance to senescence [43,44]. Moreover, DPSCs retain their regenerative potential even after cryopreservation, making them a valuable resource for tissue engineering and cell-based therapies [45]. In vitro studies have demonstrated their ability to differentiate into odontoblasts, osteoblasts, adipocytes, chondrocytes, and neuronal-like cells, highlighting their multilineage differentiation potential [46]. Preclinical and clinical studies have explored the use of DPSCs in dental pulp regeneration, dentin repair, craniofacial reconstruction, and treatment of systemic diseases, showcasing their versatility and therapeutic efficacy [47].

Regenerative potential of PDLSCs and DPSCs:

The mechanisms underlying PDLSC- and DPSC-mediated regeneration are multifaceted and involve complex interactions between cellular, molecular, and microenvironmental factors. Understanding these mechanisms is crucial for developing targeted therapies aimed at harnessing the regenerative potential of PDLSCs and DPSCs. Periodontal ligament stem cells (PDLSCs) and dental pulp stem cells (DPSCs) play pivotal roles in tissue regeneration within the oral cavity. Their regenerative potential is attributed to intricate mechanisms involving paracrine signalling, immunomodulation, and extracellular matrix remodelling. PDLSCs and DPSCs secrete a plethora of growth factors, cytokines, and chemokines that orchestrate tissue repair processes. For instance, transforming growth factor-beta (TGF-β) and bone morphogenetic proteins (BMPs) that stimulate osteogenesis and cementogenesis, promoting periodontal tissue regeneration and vascular endothelial growth factor (VEGF) which facilitates angiogenesis, enhanc-

ing tissue perfusion and cell survival[48,49].

Moreover, PDLSCs and DPSCs exert immunomodulatory effects, regulating inflammatory responses and promoting tissue homeostasis. They secrete factors such as interleukin-10 (IL-10) and indoleamine 2,3-dioxygenase (IDO), which suppress immune cell activation and dampen inflammation, fostering an environment conducive to tissue repair. Furthermore, PDLSCs and DPSCs contribute to extracellular matrix remodelling by producing matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs). This dynamic interplay between MMPs and TIMPs facilitates the turnover of extracellular matrix components, enabling tissue regeneration and functional restoration [50-52].

Periodontal ligament stem cells (PDLSCs) and dental pulp stem cells (DPSCs) have emerged as promising candidates for the treatment of neurodegenerative disorders, expanding their traditional roles beyond dental tissue regeneration. These stem cell populations possess unique properties that make them attractive for neuroregenerative therapies. Both PDLSCs and DPSCs exhibit multilineage differentiation capabilities, including the ability to differentiate into neuronal-like cells. Additionally, they secrete neurotrophic factors and anti-inflammatory molecules, creating a neuroprotective microenvironment that supports neuronal survival and function. Preclinical studies have demonstrated the efficacy of PDLSC- and DPSC-based therapies in promoting neural regeneration and functional recovery in animal models of neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and spinal cord injury. Harnessing the neuroregenerative potential of PDLSCs and DPSCs offers promising prospects for developing innovative cell-based therapies that target the underlying pathophysiology of neurodegenerative disorders, potentially leading to treatments that mitigate disease progression and enhance patient outcomes.

Neuroregenerative potential of PDLSCs and DPSCs:

DPSCs have shown promising potential for neuronal differentiation and therapeutic applications in neurological diseases [53-55]. The possibility of DPSCs to differentiate into specific neuronal types like dopaminergic neurons, spiral ganglion like neurons, and motor neurons have been studied by researchers [53-55]. Huang et al highlighted the role of insulin-like growth factor 1 (IGF-1) in enhancing the neural differentiation of DPSCs through the mTOR pathway [56]. DPSCs combined with brain-derived neurotrophic factor (BDNF)

have shown efficacy in promoting neurological recovery after stroke, indicating a potential therapeutic strategy against cerebral ischemia [57,58].

Alzheimer's Disease:

Alzheimer's disease is a progressive neurodegenerative disorder that affects millions of people worldwide. Primarily impacting older adults, Alzheimer's is characterized by the gradual deterioration of cognitive functions, memory loss, and behavioral changes. The exact cause of Alzheimer's remains unknown, but researchers believe it involves a combination of genetic, environmental, and lifestyle factors [59].

Alzheimer's disease is characterized by the accumulation of beta-amyloid plaques and tau tangles in the brain, leading to the death of nerve cells and disruption of neural communication. These changes result in brain atrophy, particularly in areas associated with memory and cognitive function. Treatment options for Alzheimer's disease focus on managing symptoms and improving quality of life. Medications such as cholinesterase inhibitors and memantine may help improve cognitive function and manage behavioral symptoms. Non-drug interventions like cognitive stimulation therapy, physical exercise, and occupational therapy can also be beneficial [60].

Research into new treatment approaches including immunotherapy, gene therapy, and lifestyle interventions is ongoing to develop more effective therapies and potentially find a cure for Alzheimer's disease[61].

A preliminary search of PubMed, the Cochrane Database of Systematic Reviews, and JBI Evidence Synthesis was conducted, revealing no current or ongoing systematic or scoping reviews on the topic. A scoping review approach was selected to map various forms of evidence within the field and identify areas requiring further research.

The primary objective of this scoping review is to identify, explore, and map the globally available evidence on the therapeutic effects of DPSC and PDLSC on Alzheimer's disease. The authors believe that the results of this scoping review will enhance healthcare professionals' understanding of the neurodegenerative and neuroprotective potential of PDLSC and DPSC, thereby equipping them to manage Alzheimer's disease more effectively. Additionally, the findings will assist governments and policymakers in devising preventive and treatment strategies and identifying gaps for future research.

Methodology:

The protocol for this scoping review was

prepared using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) and presented according to the PRISMA-ScR extension for scoping reviews[62,63]. The review followed Arksey and O'Malley's guidelines, encompassing several key steps viz [A] identifying the research question, [B] identifying relevant studies, [C] selection of eligible studies, [D] charting the data, and [E] collating, summarising, and reporting of results.

The main research question is, "What is the current evidence on the therapeutic effect of PDLSC and DPSC on Alzheimer's disease?" Sub-questions include identifying the types of studies that have examined the effects of PDLSC and DPSC on Alzheimer's disease, exploring the proposed mechanisms linking these stem cells with Alzheimer's disease management, and identifying gaps in the current literature.

Relevant studies were identified using the PCC (Population, Concept, Context) format. The population of interest includes patients with Alzheimer's disease, the concept focuses on the therapeutic effects of PDLSC and DPSC, and the context is unspecified. A preliminary search in MEDLINE helped develop a comprehensive search strategy for MEDLINE, Web of Science, and SCOPUS databases, using keywords related to stem cells, periodontal ligament, dental pulp, and Alzheimer's disease viz. Stem cells [MeSH], Periodontal ligament [MeSH], Alzheimer's disease [MeSH], Memory disorder [MeSH], Dental pulp [MeSH], Periodontal ligament stem cells [tiab], tooth derived stem cells [tiab], Dental pulp stem cells [tiab], Alzheimer's disease [tiab], Memory impairment [tiab] and Memory [tiab] using the search strategy as given in supplemental file S1. The database last searched was on 30/10/2024.

Eligible studies were selected by collating articles from the search into EndNote (ENDNOTE version 20) and removing duplicates. Titles and abstracts were screened based on inclusion criteria, which required studies on the management of Alzheimer's disease using PDLSC and DPSC, including human and animal studies and original research articles. Exclusion criteria included review articles, opinion papers, and studies without retrievable full texts. Full-text articles were assessed using the JBI SUMARI tool, with disagreements resolved through discussion. The selection process is illustrated in a PRISMA-ScR flow diagram (Figure 1 and 2).

Data extraction tools were developed and refined throughout the process, with discrepancies between reviewers resolved

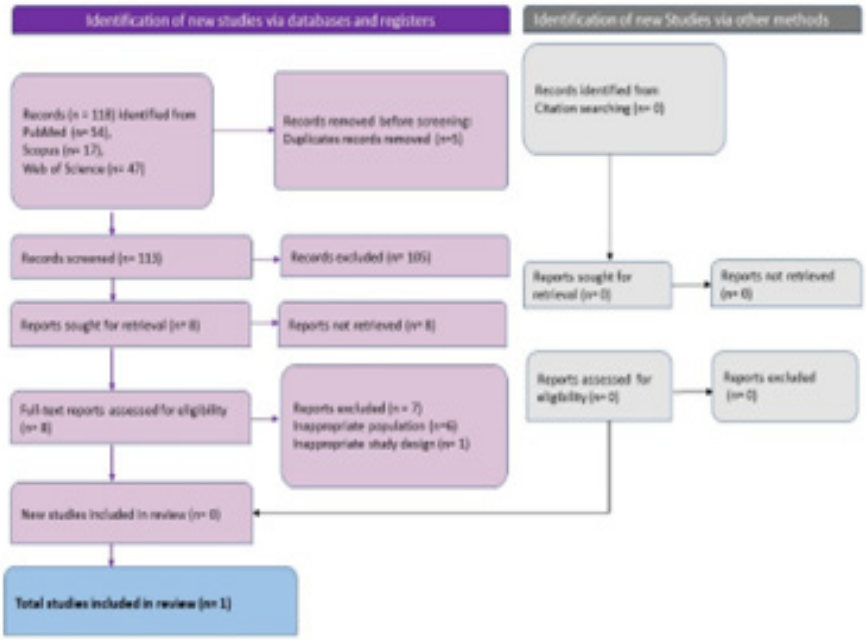


Figure 1: PRISMA-ScR chart depicting article selection for therapeutic role of PDLSC against AD

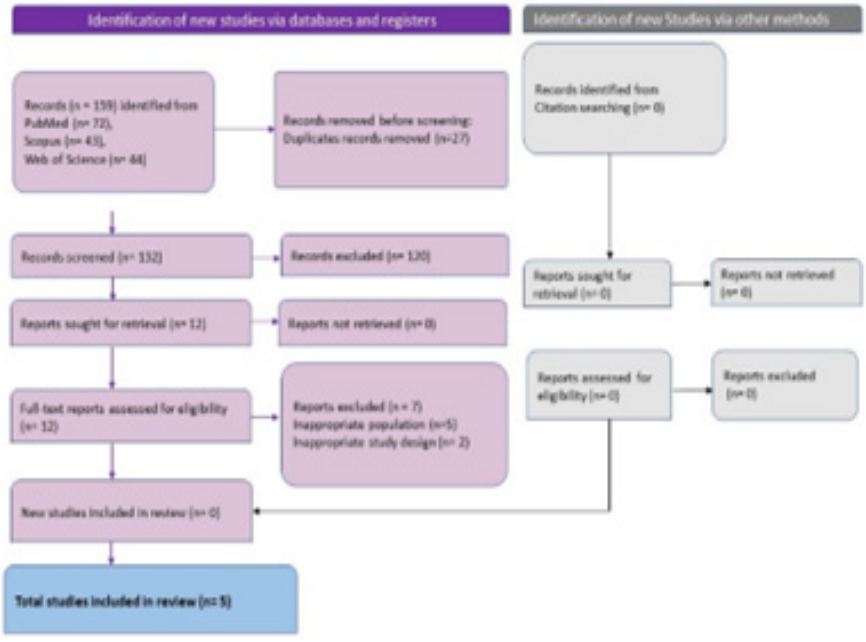


Figure 2: PRISMA-ScR chart depicting article selection for therapeutic role of DPSC against AD

through discussion. The extracted data were summarized in table 1 and 2, with narrative descriptions addressing the research questions and study objectives.

Results and Discussion:

Overview of results:

Database search revealed 159 studies for DPSC and 118 studies for PDLSC. After

duplicates removal, 132 unique studies remained for DPSC and 113 for PDLSC. Following title and abstract screening, 120 and 105 studies were excluded for DPSC and PDLSC respectively. 12 and 8 studies were sought for full text retrieval for DPSC and PDLSC respectively. After full text screening, 5 studies for DPSC and one study for PDLSC which adhered to the eligibility criteria were included in the review (Figure 1 and 2) [64-69]. The selected articles were published between 2009 to 2024. Out of the selected 5 articles for DPSC, 3 (60%) were conducted in China[65,66,69], one (20%) in Brazil [67], and one (20%) in Japan[68]. The study for PDLSC was conducted in Iran[64]. All of the included studies were conducted in in vivo animal model[69] or invitro cellular model [65,67,68] or both [64,66]. All of the selected studies were of the experimental study design (Table 1).

Alzheimer's disease model used:

Amyloid beta induced Alzheimer's disease model was the most commonly used AD model in three out of the six selected studies [67-69]. Streptozotocin (STZ) induced Alzheimer's disease rat model was used by Mohebichamkhorami et al., 2022[64] and Okadaic acid (OA)-induced damage was used as AD cellular model by Wang et al., 2017 [65]. Transgenic mouse model, 3xTg-AD mice was employed by Xiong et al., 2024 [66]. STZ administration in rodents leads to the manifestation of several AD hallmarks, including memory/learning disturbances, amyloid-β accumulation, tau hyperphosphorylation, oxidative stress, and brain glucose hypometabolism, closely resembling the pathophysiological features of sporadic AD [70]. Furthermore, STZ has been shown to induce neuronal apoptosis, synaptic loss, and tau hyperphosphorylation by increasing phosphorylation of the mitochondrial fission protein Drp1, thereby promoting mitochondrial fragmentation in hippocampal neurons, which are key pathological mechanisms in AD progression [71]. OKA induced neurotoxicity is tool to study Alzheimer's disease pathology. OKA induces neurodegeneration along with tau hyperphosphorylation, GSK3β activation, oxidative stress, neuroinflammation, and neurotoxicity, all of which are characteristic features of Alzheimer's disease pathology [72]. 3xTg-AD is a triple-transgenic model that has been developed to express three key genes associated with familial Alzheimer's disease (AD) — APPSwe, PS1M146V, and tauP301L — in a way that mirrors their expression in human AD patients [73-75] (Table 1).

S no	Author	Year	Country	invitro culture/ invitro animal model	Study Population/Cluster	Aim/objective	Stem cell isolation/culture method	Type of study
DPSC								
1	Apel et al. [67]	2009	Brazil	In vitro culture	amyloid beta peptide 1-42 (Ab1-42) induced Alzheimer's disease model of primary cultures of hippocampal and ventral mesencephalic neurons from Wistar rats	To investigate the neuroprotective effect of dental pulp cells (DPCs) in in vitro models of Alzheimer and Parkinson disease	Isolation of DPSC from adult rat incisors. Primary cultures of hippocampal and ventral mesencephalic neurons were used	experimental study
2	Zhang et al. [69]	2021	China	In vivo animal model	human Aβ1–42 induced Alzheimer's disease model of rats	To assess the effects of dental pulp stem cells on the expression of neuron-related proteins in the hippocampus, as well as on cognitive and behavioral abilities in the rat model of Alzheimer's disease	Dental pulp stem cells (DPSCs) were isolated from pulpal cavities of rat incisors and cultured to the third generation	experimental study
3	Wang et al. [65]	2017	China	In vitro cell line	Okadaic acid (OA)-induced damage to human neuroblastoma cell line, SH-SY5Y - AD cellular model	To investigate the therapeutic potential of dental pulp stem cells in promoting the regeneration of damaged neuron cells in Alzheimer's disease.	Dental pulp stem cells (DPSCs) were isolated from pulpal cavities normal human third molars extracted from patients of age 19 -26 years. Cultured cells were isolated based on their ability to form colonies and passages 2-3 of isolated cells were selected for the study	experimental study
4	Xiong et al. [66]	2024	China	in vitro cellular model and in vivo animal model	Transgenic mouse model, 3xTg-AD mice and BV2 and HT22 cells		Dental pulp isolated from healthy normal extracted third molar from healthy volunteers of age 20-30 years and cultured to obtain hDPSC	experimental study

5	Ahmed et al. [68]	2016	Japan	In vitro cell line	Amyloid beta (Aβ1–42) induced neurotoxicity in Human neuroblastoma SH-SY5Y cells	To investigated the therapeutic potential of secretome derived from DPSCs to reduce cytotoxicity and apoptosis caused by amyloid beta (Aβ) peptide by 1. Characterization of the DPSC secretome and comparison to the secretomes of bone marrow-derived mesenchymal stem cells (BMSCs) and adipose-derived stem cells (ADSCs). 2. Evaluation of the neuroprotective effects of the DPSC secretome against amyloid-beta (Aβ)-induced neurotoxicity in SH-SY5Y cells. 3. Investigation of the antiapoptotic mechanisms of the DPSC secretome, such as upregulation of Bcl-2 and downregulation of Bax. 4. Identification of the presence and Aβ-degrading ability of the enzyme neprilysin (NEP) in the DPSC secretome.	Dental pulp isolated from healthy normal extracted third molar from healthy volunteers of age 20-28 years and DPSc secretome prepared	experimental study
PDLSC								

6	Mohebi-chamkhora-mi et al. [64]	2022	Iran	in vitro cellular model and in vivo animal model	Streptozotocin induced Alzheimer's disease rat model - brain homogenate and C6 glioma cell culture	1. To investigate the effect of brain homogenate of a rat model of AD (BH-AD) on the enhancement of protein secretion in the secretome of periodontal ligament stem cells (PDLSCs) when cultured in a 3D environment. 2. To examine the effect of f this modified secretome on neural cells to study the impact of the conditioned medium (CM) on stimulation of regeneration or immunomodulation in AD.	PDLSCs were isolated by the explant culture of tooth samples, differen-tiated in adipogenic and osteogenic differentiation mediums and harvested at the third passage and cultured for 3D spheroid formation. Conditioned media of were then prepared from PDLSC spheroids, with and without exposure to brain homogenate from an Alzheimer's disease (AD) rat model (BH-AD).	experi-mental study

Table 1: Study characteristics

Key findings from the included studies:

Dental pulp stem cells (DPSCs) and human DPSCs (hDPSCs) exhibit promising therapeutic potential for Alzheimer's disease (AD) by exhibiting a range of neuroprotective and regenerative effects. Co-culture with DPSCs significantly attenuated amyloid-beta (Aβ)-induced toxicity in primary hippocampal neurons and promoted neuronal viability through the secretion of neurotrophic factors like NGF, GDNF, BDNF, and BMP2 [67]. Transplantation of DPSCs into the hippocampus of AD rodents improved cognitive and behavioral functions, enhancing the secretion of neuron-related proteins [69]. hDPSCs further demonstrated the ability to enhance the viability of AD model cells, promote the restoration of neuronal morphology, and suppress the pathological phosphorylation of Tau protein. The neuroprotective mechanisms of hDPSCs involve the activation of the AKT-GSK3β-Nrf2 signaling pathway, leading to antioxidant and neuroregenerative effects [65,66]. The DPSC secretome also exerted beneficial effects, including preserving cell morphology, modulating apoptosis, and containing higher levels of the Aβ-degrading enzyme neprilysin [68]. Collectively, these findings highlight the multifaceted therapeutic potential of DPSC-based approaches in tackling the complex pathology of Alzheimer's disease.

The periodontal ligament stem cell (PDLSC) secretome exhibits promising therapeutic potential for Alzheimer's disease (AD) through multiple mechanisms. The PDLSC secretome may exert anti-inflammatory and antiapoptotic effects, which could be beneficial in the context of AD. Additionally, the secretome contains neurotrophic factors, such as BDNF and NGF, that can promote neuroregeneration and neuroprotection, potentially aiding in AD treatment. Notably, the PDLSC secretome includes proteins like SHP-1 and PYGM, which are involved in nerve regeneration and glycogen metabolism, respectively, suggesting additional pathways through which the secretome may exert its therapeutic effects. Importantly, the therapeutic potential of PDLSCs in AD appears to be primarily mediated through the paracrine factors secreted in their conditioned medium, rather than their direct differentiation capacity. These findings highlight the multifaceted therapeutic potential of the PDLSC secretome and its promise as a cell-free approach for addressing the complex pathology of Alzheimer's disease[64] (Table 2).

S no	Author.(Year)	Year	Neurotrophic factors produced	Behavioural changes	Mechanism reported (Yes/No)	Mechanism findings	Gaps reported in the study	Key findings	Comments
DPSC									
1	Apel et al. [67]	2009	nerve growth factor (NGF), glial cell-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF), and bone morphogenetic protein 2 (BMP2)	Not studied	yes	Despite the prevention of direct contact between neurons and DPCs in the experimental setup, the observed neuroprotection indicates that secreted factors, possibly neurotrophins produced by the DPCs, are responsible for the protective effects.	1. DNA microarray technology is limited to studying gene expression at the mRNA level, which may not necessarily correlate with protein levels. 2. The study did not include replications, which could have provided more robust and reliable results. 3. Variations deriving from heterogeneous cell populations may have influenced the gene expression profiles identified in the study.	1. The co-culture with DPCs significantly attenuated the toxicity induced by Ab1-42 in the primary cultures of hippocampal neurons. 2. DPCs led to an increase in neuronal viability in untreated cultures, suggesting a neurotrophic effect in the Alzheimer's model. 3. Human dental pulp cells expressed a neuronal phenotype and produced neurotrophic factors such as nerve growth factor (NGF), glial cell-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF), and bone morphogenetic protein 2 (BMP2)	DPCs could potentially be explored as a novel therapeutic approach for Alzheimer's disease.

2	Zhang et al. [69]	2021	DPSC transplantation promotes the secretion of neuron-associated proteins	Improved the cognitive and behavioral abilities of AD rats in radial arm maze test	yes	1. DPSC transplantation increases the expression of neuron-associated proteins such as doublecortin (DCX) and NeuN in the brain, which are essential for neurogenesis and neuronal function. 2. Secretion of neurotrophic factors such as brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and neurotrophin-3, which promote neurological function recovery. 3. Differentiated DPSCs promote axonal regeneration through the action of chemokines and their receptors, enhancing neural plasticity. 4. DPSCs transplanted into the brain can express neuron-specific markers and exhibit characteristics of neurons, indicating their potential to differentiate into neuronal cells.	1. While the study demonstrated the therapeutic ability of DPSCs in improving cognitive and behavioral functions in Alzheimer's disease rats, the specific mechanisms underlying these effects were not fully elucidated. Further research is needed to determine the precise mechanisms by which DPSC transplantation exerts its neuroprotective and regenerative effects. 2. The study highlighted the challenge of translating the findings to clinical applications, especially in elderly patients with Alzheimer's disease who may have multiple comorbidities.	The transplantation of DPSCs into the hippocampus of rats with Alzheimer's disease resulted in improved cognitive and behavioral functions. DPSC transplantation promoted the secretion of neuron-related proteins in the rats and enhanced their cognitive abilities	The study highlighted the potential of DPSCs in treating neurological disorders like Alzheimer's disease

3	Wang et al. [65]	2017	Not studied	Not studied	yes	The study showed that hDPSCs suppressed the phosphorylation at Ser 396 of Tau protein, which is associated with Alzheimer's disease pathology . By antagonizing Tau phosphorylation, hDPSCs may help maintain the stability of the nervous system and promote the regeneration of damaged neuron cells in Alzheimer's disease.	1. The study noted that the isolated hDPSCs in the research had relatively low expression of STRO-1, which may be associated with the isolation method and the cell states of the hDPSCs. 2. Further research is required to evaluate the efficacy of hDPSC treatment in vivo using animal models.	1. hDPSCs promoted the regeneration of damaged neuron cells in the Alzheimer's disease cellular model. 2. Treatment with hDPSCs resulted in a significant increase in cell viability and a decrease in apoptosis of the model cells. 3. Observation of DiI labeling showed prolonged dendrites in hDPSCs-treated cells compared to retracted dendrites in the Alzheimer's disease model cells. 4. Specific staining of α-tubulin and F-actin demonstrated that hDPSCs-treated cells exhibited the morphology of restored neurons, with elongated dendrites and well-organized cytoskeletal components. 5. Western blotting revealed that phosphorylation at Ser 396 of Tau protein, associated with Alzheimer's disease pathology, was significantly suppressed by the addition of hDPSCs	hDPSCs have the potential to promote the regeneration of damaged neurons and may serve as a valuable cell source for the treatment of Alzheimer's disease

4	Xiong et al. [66]	2024	Not studied	hDPSCs enhanced spatial learning and memory ability in 3xTg-AD mice	yes	1. Activation of the AKT/GSK3β-mediated Nrf2 pathway. This pathway led to Nrf2 activation and nuclear accumulation, resulting in antioxidant and neuroprotective effects . 2. By promoting Nrf2 nuclear accumulation and downstream antioxidant enzyme expression, hDPSCs helped maintain oxidative stress homeostasis in the brain, contributing to neuroprotection and cognitive enhancement. 3. hDPSCs mediated neuroprotective effects by regulating the polarization of hyperreactive microglia cells and promoting the recovery of damaged neurons. 4. Anti-inflammatory and neuroreparative action of hDPSCs contributed to the improvement in cognitive function and neuropathological features in AD mice	1. Lack of clarity on how hDPSCs stimulate AKT to activate Nrf2 function, indicating a gap in the understanding of the specific molecular mechanisms underlying the therapeutic effects of hDPSCs. 2. Uncertainty regarding the multi-target therapeutic pathways of hDPSCs in improving cognitive ability in AD mice, suggesting the need for a deeper understanding of the mechanisms involved.	1. hDPSCs demonstrated neuroprotective effects by improving oxidative stress and promoting neurorepair in in vitro AD models. 2. Transplantation of hDPSCs in 10-month-old 3xTg-AD mice resulted in significant improvements in cognitive function and neuropathological features. 3. The therapeutic effects of hDPSCs were mediated, at least partially, by the activation of the AKT-GSK3β-Nrf2 signaling pathway, leading to antioxidant and neuroprotective effects. 4. hDPSCs reshaped the neuropathological microenvironment in both in vitro and in vivo AD models, highlighting their potential as a therapeutic candidate for AD	Findings corroborated the neuroprotective capacity of hDPSCs to reshape the neuropathological microenvironment in both in vitro and in vivo AD models, which may be a tremendous potential therapeutic candidate for Alzheimer's disease.

5	Ahmed et al. [68]	2016	1. DPSC secretome contains the following cytokines/growth factors: EGF, FGF-2, FLT-3L, FRACTALKINE, GM-CSF, PDGF-BB, INFα2, INF GAMMA, IL-12p40, -13, -15, -17, -1ra, -1ALPHA, -1BETA, and -(2–10)2, MDC, MIP--α, MIP-1beta, MCP-1, MCP-3, **PDGF-AA,** CCL5, IP-10, sCD40L, TNFα, TNFbeta, and VEGF. 2. DPSC secretome contains higher concentrations of VEGF, RANTES, FRACTALKINE, FLT-3, GM-CSF, and MCP-1 than both BMSC and ADSC secretomes	Not studied	yes	1. The DPSC secretome was found to have an antiapoptotic effect by: Stimulating the endogenous survival factor Bcl-2 and decreasing the apoptotic regulator Bax. 2. DPSC secretome contains the enzyme neprilysin (NEP), which degrades amyloid-beta (Aβ) in vitro thereby contributing to the clearance of Aβ accumulation in the brain	Not reported	1. DPSC secretome treatment preserves morphology and improves the viability of SH-SY5Y Cells. 2. DPSC secretome has an antiapoptotic effect by stimulating the endogenous survival factor Bcl-2 and decreasing the apoptotic regulator Bax, revealing the possible mechanism of neuroprotection. 3. NEP expression was significantly increased in DPSC secretome compared to that in both BMSC and ADSC secretomes indicating the stronger potential of DPSCs to degrade Aβ1–42 protein. 4. Neurodifferentiated SH-SY5Y exposed to Aβ1–42 and treated with DPSC secretome kept their morphology and viability compared to nontreated cells.	DPSCs may serve as a promising source for secretome-based treatment of Alzheimer's disease

PDLSC									
6	Mohebichamkhorami et al. [64]	2022	SHP-1, an inducer of neural differentiation	Not studied	yes	1. PDLSC secretome may have anti-inflammatory and antiapoptotic effects, which could be beneficial in the context of AD. 2. Neurotrophic factors can promote neuroregeneration and neuroprotection, which could be valuable for AD treatment. 3. SHP-1 is known to play a role in nerve regeneration, while PYGM is involved in glycogen metabolism, suggesting potential mechanisms for the PDLSC secretome's therapeutic effects in AD.4. Therapeutic potential of PDLSCs in AD may be primarily mediated through the paracrine factors secreted in their conditioned medium (CM), rather than their direct differentiation potential.	Not reported	1. Crosstalk between PDLSCs and BH-AD have additive effects in releasing more efficient neuroreparative secretomes. 2. The CM was enriched with SHP-1 as an inducer of neural differentiation, which is involved in anti-inflammatory processes. 3. PYGM (as a glycogenolysis enzyme) was overexpressed in this modified secretome which can be involved in neural regeneration due to supporting energy requirements in the AD brain.	The modified secretome derived from 3D cultured spheroids of PDLSCs treated by BH-AD as a reservoir of regenerating neural factors can serve as a potential source for AD treatment.

Table 2: Relevant findings from the included studies.

Potential mechanism of therapeutic effect of PDLSC against AD:

The authors of the included article suggest that the paracrine-mediated effects of the PDLSC secretome, including modulation of inflammation, apoptosis, and provision of neurotrophic factors, as well as specific proteins involved in nerve regeneration and glycogen metabolism, may contribute to the therapeutic potential of PDLSCs in Alzheimer's disease[64] (Table 2).

The therapeutic potential of PDLSCs in AD may be primarily mediated through the paracrine factors secreted in their conditioned medium (CM), rather than their direct differentiation potential. PDLSCs have been shown to possess promising potential of neural damage therapy which was paracrine mediated [76]. PDLSC secretome contains a broad spectra of secreted neurotrophic factors such as BDNF, VEGFA, NT-3, NGF, and GDNF. These neurotrophic factors can promote neuroregeneration and neuroprotection, which could be valuable for AD treatment. PDLSC-CM was found to be beneficial in spinal cord injury by promoting long-term neuroregeneration [77]. PDLSC secretome may have anti-inflammatory and antiapoptotic effects, which could be beneficial in the context of AD. In pathological conditions, the PDLSC secretome can inhibit pro-inflammatory responses, suppress apoptosis, and stimulate the differentiation of tissue-specific precursor cells via paracrine signalling [78].

The proteomic analysis of the PDLSC secretome revealed the presence of proteins like Src-homology 2 domain (SH2)-containing PTPs (SHP-1) and muscle glycogen phosphorylase (PYGM). SHP-1 is known to play a role in nerve regeneration, while PYGM is involved in glycogen metabolism, suggesting potential mechanisms for the PDLSC secretome's therapeutic effects in AD.SHP-1 is a multifunctional signalling protein highly expressed in the cortex, cerebellum, and cervical spinal cord, playing a key role in CNS development. It regulates astrocyte and oligodendrocyte differentiation and survival, affecting myelination and neuroinflammation[79,80]. SHP-1 is involved in neurotransmission, axon regeneration, and neuronal signalling, interacting with synaptophysin and promoting the PKC/PLD1 cascade [79,81]. It modulates inflammation and supports photoreceptor survival by regulating chemokine expression and nitric oxide production [82]. Additionally, SHP-1 influences hematopoietic progenitor cell differentiation, cell proliferation, and immune response regulation[64].

PYGM is essential for glycogen metabolism in the brain, catalysing glycogenoly-

sis and releasing glucose-1-phosphate [83]. Reduced PYGM and its regulator RAC1 are observed in astrocytes of schizophrenia patients and in the lesioned hemisphere of a teleost fish model [84,85]. In Alzheimer's disease, a deficit in glucose metabolism is noted, indicating that exogenous PYGM from PDLSCs-derived CM was prepared in the presence of BH-AD (PDLSC-HCM) might help sustain energy requirements, potentially alleviating some pathological effects [64,86].

Potential mechanism of therapeutic effect of DPSC against AD:

The proposed mechanisms which contribute to the therapeutic potential of DPSCs/hDPSCs in Alzheimer's disease involve paracrine-mediated neuroprotection and neuroregeneration, modulation of Tau phosphorylation, activation of antioxidant pathways, regulation of microglia and inflammation, as well as antiapoptotic effects and Aβ clearance [65-69] (Table 2).

Paracrine-mediated neuroprotection and neuroregeneration:

DPSCs secrete neurotrophic factors such as BDNF, NGF, and neurotrophin-3, which promote neurological function recovery and neural plasticity[87,88]. BDNF (Brain-Derived Neurotrophic Factor) promotes neurological function recovery by supporting the survival and growth of neurons. It enhances neural plasticity by facilitating synaptic formation and strengthening connections between neurons. BDNF also plays a crucial role in learning, memory, and cognitive function [89,90]. NGF (Nerve Growth Factor) and neurotrophin-3 plays a crucial role in neurological function recovery and neural plasticity by promoting the growth, survival, and maintenance of neurons. It enhances synaptic plasticity, facilitating learning and memory processes. Additionally, NGF supports axonal regeneration after injury, aiding in neural repair and recovery [91,92].

DPSCs can increase the expression of neuron-associated proteins like doublecortin and NeuN, which are essential for neurogenesis and neuronal function[69]. NeuN, also known as Fox3, is a member of the Fox1 gene family and regulates RNA splicing. NeuN plays a predominant role in nerve tissue development and nerve function regulation[93,94]. It plays a crucial role in synaptic formation and functional regulation in the hippocampus. Dysfunction of NeuN is associated with neurodevelopmental retardation, cognitive impairment, and defects in synaptic plasticity[95]. On the other hand, Doublecortin (DCX) is a microtubule-associated protein which is crucial for neuron generation and migra-

tion. It coordinates microtubule functions, including cell movement, transport, polarity, and mitosis, making it the gold standard marker for neurogenesis [96]. In DCX knockout mice, the pyramidal cells in the hippocampal CA3 region are abnormal, disrupting the neural network and function of the hippocampus [97]. DPSCs can also differentiate into neuronal cells and express neuron-specific markers, indicating their potential to replace damaged neurons [98].

Modulation of Tau phosphorylation:

hDPSCs can suppress the phosphorylation of Tau protein at Ser396, which is associated with AD pathology, helping to maintain the stability of the nervous system and promote the regeneration of damaged neurons [65]. Suppression of tau phosphorylation helps Alzheimer's disease (AD) by reducing the formation of neurofibrillary tangles, which are aggregates of hyperphosphorylated tau protein commonly found in the brains of individuals with AD. These tangles interfere with neuronal function and contribute to neurodegeneration. By inhibiting tau phosphorylation, the progression of neurodegeneration and cognitive decline associated with AD can be slowed or potentially halted [99].

Activation of the AKT/GSK3β-mediated Nrf2 pathway:

hDPSCs can activate this pathway, leading to Nrf2 nuclear accumulation and enhanced expression of antioxidant enzymes, resulting in antioxidant and neuroprotective effects [66]. Increased levels of antioxidant enzymes in the brain help prevent cognitive decline by reducing oxidative stress-induced damage to neurons and other brain cells. Oxidative stress, caused by an imbalance between the production of reactive oxygen species (ROS) and the body's ability to detoxify them, can lead to cellular damage and contribute to neurodegenerative diseases like Alzheimer's [100]. Antioxidant enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase neutralize ROS, protecting neurons from oxidative damage and preserving cognitive function. This helps maintain oxidative stress homeostasis in the brain, contributing to neuroprotection and cognitive enhancement [101].

Regulation of microglial polarization and inflammation:

hDPSCs can mediate neuroprotective effects by regulating the polarization of hy-

perreactive microglia cells and promoting the recovery of damaged neurons [100]. The anti-inflammatory and neuroreparative actions of hDPSCs contribute to the improvement in cognitive function and neuropathological features in AD models.

Antiapoptotic effects and Aβ clearance:

The DPSC secretome has an antiapoptotic effect by stimulating the endogenous survival factor Bcl-2 and decreasing the apoptotic regulator Bax [68]. Bcl-2 stands out as a pivotal antiapoptotic factor crucial for promoting cell survival, contrasting with Bax, a proapoptotic factor driving apoptosis and cell demise. Bcl-2 effectively suppresses Bax-triggered apoptosis, prolongs the delay in caspase expression, and boosts neuronal survival [102]. The DPSC secretome contains the enzyme neprilysin (NEP), which can degrade amyloid-beta (Aβ) in vitro, thereby contributing to the clearance of Aβ accumulation in the brain [68].

Limitations within literature:

The key gaps and limitations reported in the included articles relate to the limitations of the therapeutic effects of DPSCs and hDPSCs, the challenges in translating the findings to clinical applications, and the need for more in-depth characterization and understanding of the specific molecular and cellular mechanisms involved in the observed therapeutic benefits (Table 2).

Limitations of DNA microarray technology:

DNA microarray technology is confined to mRNA-level gene expression analysis, potentially diverging from protein levels. Lack of replications in the study limits result reliability, while variations within cell populations may have influenced gene expression profiles [67].

Mechanistic gaps in DPSC therapy for Alzheimer's disease: Zhang et al., 2021 showcased DPSCs' therapeutic potential in enhancing cognitive and behavioural functions in Alzheimer's disease-afflicted rats, yet the exact mechanisms remain unclear. Further investigation is essential to delineate how DPSC transplantation confers neuroprotective and regenerative benefits. Translating these findings into clinical settings, particularly for elderly Alzheimer's patients with multiple comorbidities, poses a significant challenge, underscoring the need for comprehensive research and tailored approaches [69] .

Limitations in hDPSC characterization:

Wang et al., 2017 observed that the hDPSCs isolated for research displayed relatively low STRO-1 expression, potential-

ly linked to the isolation method and the cells' states. Additional research is necessary to assess the in vivo efficacy of hDPSC treatment using animal models [65].

Gaps in understanding the mechanisms of hDPSC action: The mechanism by which hDPSCs stimulate AKT to activate Nrf2 function remains unclear, highlighting a gap in understanding the precise molecular pathways behind the therapeutic effects of hDPSCs. The complexity of the multi-target therapeutic pathways of hDPSCs in enhancing cognitive ability in AD mice underscores the necessity for a more profound exploration of the involved mechanisms [66].

Strengths and limitations of the review:

The scoping review followed established guidelines like PRISMA-ScR and Joanna Briggs Institute, ensuring a rigorous and standardized methodology [62,63]. It offers a synthesized and up-to-date overview of the potential therapeutic role of dental pulp stem cells (DPSCs) and periodontal ligament stem cells (PDLSCs) in Alzheimer's disease (AD), aiding in assessing the feasibility of a future systematic review. Additionally, the review identified key methodological limitations in many of the included studies, providing a comprehensive assessment of the existing evidence. However, the study is not without limitations. The absence of a risk of bias assessment in this scoping review implies caution is necessary when interpreting the findings. Restricted solely to peer-reviewed material, the review may have overlooked pertinent data from less accessible sources like conference abstracts, possibly introducing publication bias. A comprehensive systematic review, considering a broader range of sources, would be necessary to ensure no relevant findings were missed due to the limited number of studies included.

Future directions:

The future directions for harnessing the therapeutic potential of dental pulp stem cells (DPSCs) and periodontal ligament stem cells (PDLSCs) against Alzheimer's disease (AD) are multifaceted. Researchers should explore the anti-inflammatory and antiapoptotic effects of the PDLSC secretome and how these may be beneficial in the context of AD. Capitalizing on the ability of DPSC and PDLSC secretomes to secrete neurotrophic factors, such as NGF, GDNF, BDNF, and BMP2, will be crucial for promoting neuroregeneration and neuroprotection. Elucidating the specific mechanisms of action, including the roles of proteins like SHP-1 in nerve regeneration and PYGM in glycogen metabolism present in the PDLSC secre-

tome, will provide deeper insights into their therapeutic effects. Evaluating the in vivo efficacy and addressing the challenges in translating these findings to clinical applications, particularly in elderly AD patients with multiple comorbidities, will be essential. Optimizing the stem cell isolation and culture conditions to enhance the neuroprotective and neuroregenerative properties of DPSCs and PDLSCs is another critical area of investigation. Finally, exploring the potential of combining DPSC and PDLSC-based therapies to achieve synergistic effects could lead to more effective, targeted, and clinically translatable stem cell-based interventions for Alzheimer's disease.

Conclusion:

This scoping review highlights the emerging evidence supporting the therapeutic potential of dental pulp stem cells (DPSCs) and periodontal ligament stem cells (PDLSCs) in Alzheimer's disease (AD). The reviewed studies demonstrate the multifaceted neuroprotective and neuroregenerative effects of these stem cells and their secreted factors. DPSCs and PDLSCs exhibit protective effects against amyloid-beta toxicity, promote neuronal viability, and enhance cognitive and behavioural functions in AD models. Further research is warranted to elucidate the precise mechanisms, optimize the stem cell-based interventions, and evaluate their long-term efficacy and clinical translatability. Harnessing the regenerative and neuroprotective capabilities of DPSCs and PDLSCs holds promise for developing innovative and effective therapies for Alzheimer's disease.

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